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(71) Applicant
**Alza Corporation,
950 Page Mill Road, Palo Alto, California 94304-0802,
United States of America**

(72) Inventors
**Robert M. Gale,
Victor Goetz,
Eun S. Lee,
Lina T. Taskovich,
Su Il Yum**

(74) Agent and/or Address for Service
**F. J. Cleveland & Company, 40-43 Chancery Lane,
London WC2A 1JQ**

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A5B

(54) **Transdermal administration of fentanyl**

(57) Transdermal delivery systems for delivery of fentanyl and its analgetically effective derivatives for extended periods of time are disclosed in which a skin-adhesive patch incorporates a reservoir delivers the base form of the drug at a rate of 0.5 to 10 $\mu\text{g}/\text{cm}^2/\text{hr}$ through the skin for a substantial portion of its useful life. The systems can be from 5-100 cm^2 in releasing surface and preferably employ an in-line amine resistant skin adhesive. Preferred rate controlled systems utilize an aqueous ethanolic gel in the reservoir to minimize drug content.

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FIG. 1

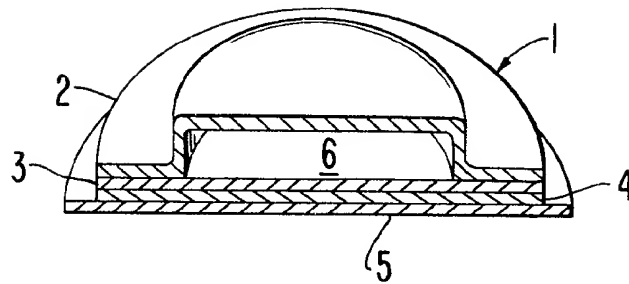


FIG. 2

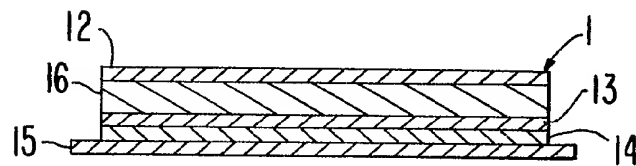


FIG. 3

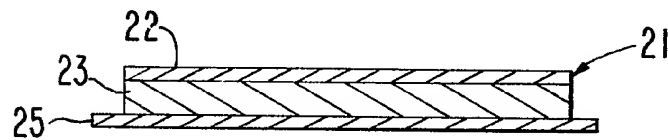
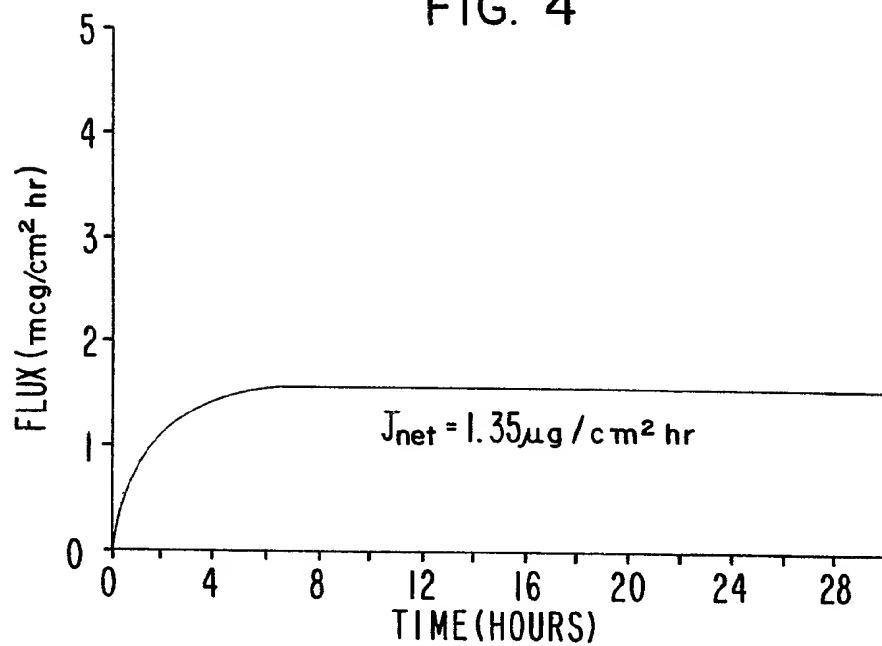


FIG. 4



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FIG. 5

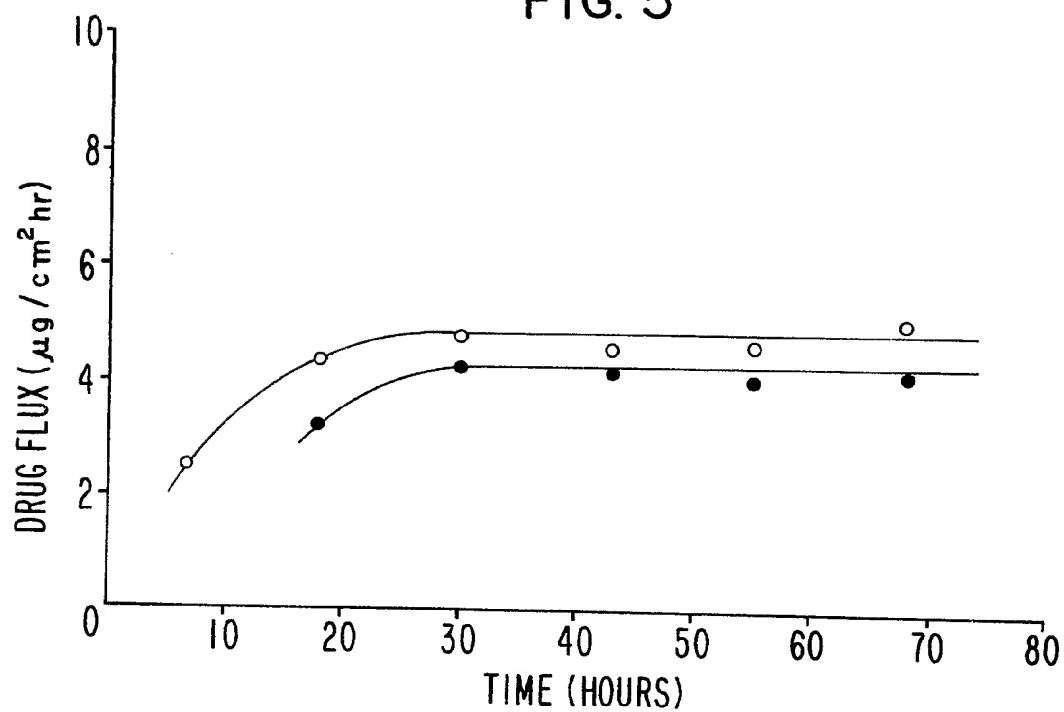


FIG. 6

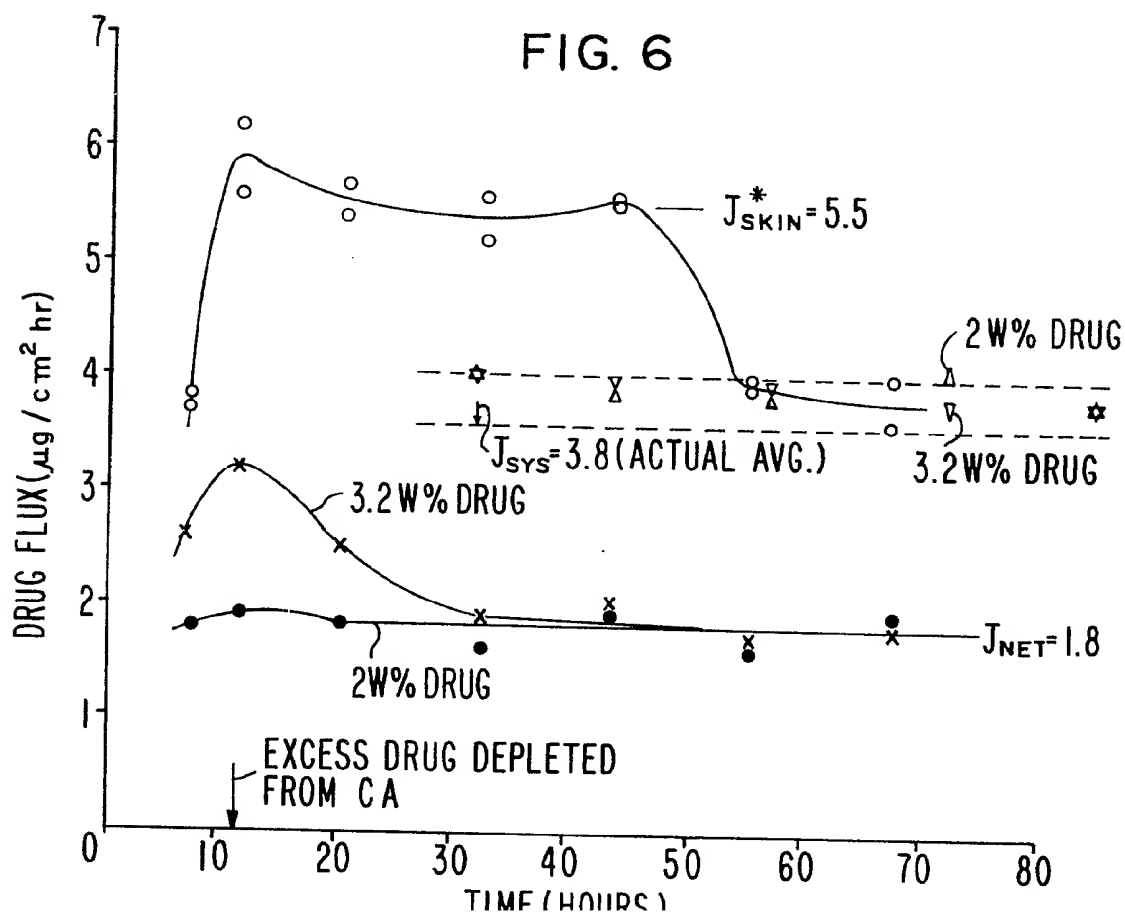


FIG. 7

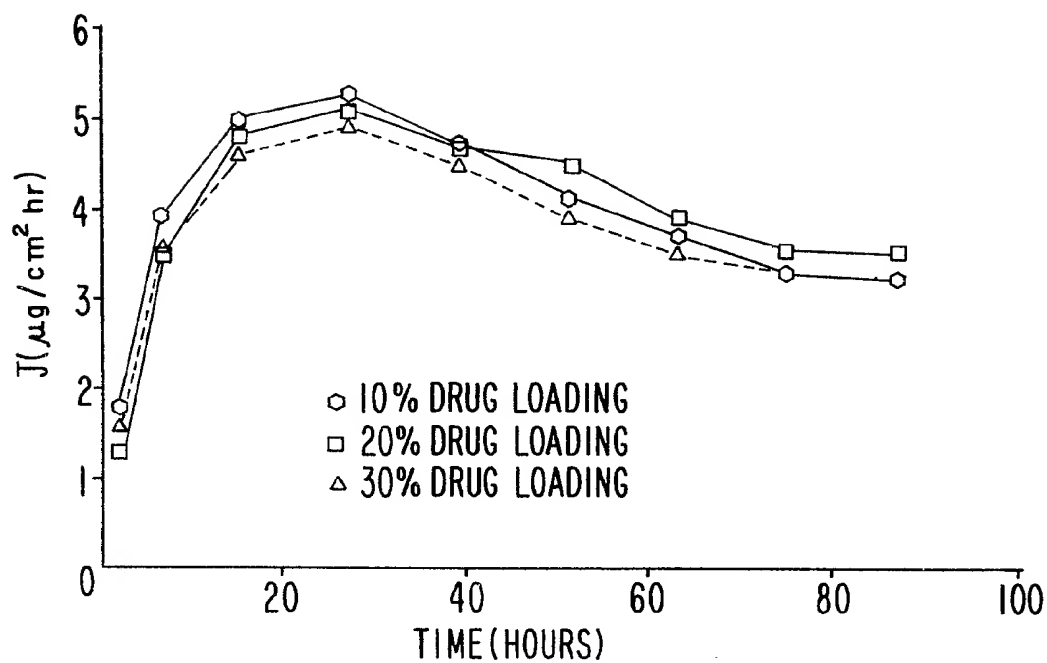
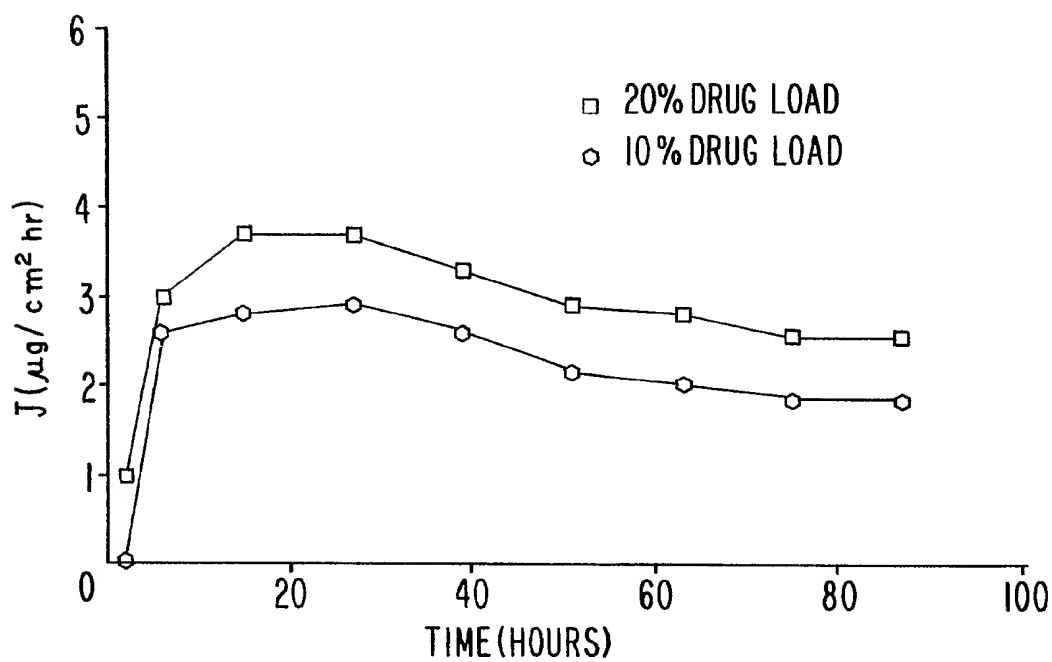


FIG. 8



SPECIFICATION

Transdermal administration of fentanyl and device therefor

5 *Field of invention*

This invention relates to the administration of fentanyl for analgetic purposes and more particularly to a method and device for administering fentanyl to a subject through intact skin over an extended period of time at a substantially constant rate.

10 *Background of the invention*

Fentanyl and its analgetically effective derivatives (hereafter referred to as "derivatives") such as sufentanyl, carfentanyl, lofentanyl and alfentanyl have long been known as extremely potent and effective anesthetics and analgesics. Fentanyl is described in U.S. Patent 3164600 and its use as approved by the FDA in the United States is described in the 1984 Physician's Desk Reference, pages 1027 through 1029 with reference to the drug SUBLIMAZE® manufactured by McNeil Lab for Janssen Pharmaceutica, Inc. In use, fentanyl is normally administered as the citrate either as a bolus injection or infusion or a continuous infusion for the purposes of producing anesthesia or analgesia.

The application of transdermal drug delivery technology to the administration of a wide variety of drugs has been proposed and various systems for accomplishing this are disclosed in numerous technical journals and patents. U.S. Patent No. 3598122, 4144317, 4201211, 4262003, and 4379454, are representative of various transdermal drug delivery systems of the prior art, which systems have the ability of delivering controlled amounts of drugs to patients for extended periods of time ranging in duration from several hours to several days. None of the above patents nor any other prior art of which the inventors are aware describes a transdermal delivery system which is intended to deliver fentanyl or its derivatives nor are they aware of data on skin permeability or therapeutic transdermal delivery rates adequate to design such a system. Furthermore, fentanyl and its derivatives have certain unique characteristics which impose a combination of restraints on a transdermal delivery system which have hitherto not been addressed in other systems.

Fentanyl and its derivatives are highly potent, rapidly metabolized drugs having a relatively narrow therapeutic index which produce extremely undesirable side effects on overdosage, most notably respiratory depression, which if left unchecked can cause death. They are also relatively expensive and have a high potential for abuse. We have found that these characteristics impose numerous and sometimes conflicting design constraints on a practical transdermal delivery device. For example, it would be desirable that the device deliver the drug at a substantially constant rate for at least about 24 hours while at the same time keeping the amount of drug within both the unused and depleted systems to a minimum. Another example of conflicting constraints is that the degree to which the system controls the release rate should be relatively high in order to assure that excessive amounts of the drug are not delivered in the event that the skin of a patient has been damaged or has an abnormally high permeability. But the release rate per unit area of system cannot be selected at such a low level that the onset of analgesia is delayed beyond five hours or that adequate dosages are not obtained from reasonably sized systems. In addition to these general design criteria we have discovered certain properties of fentanyl, and its derivatives such as skin permeability and drug binding in the skin which impose additional conflicting design constraints.

According to our invention we have provided methods for the transdermal delivery of fentanyl or its derivatives and transdermal delivery systems for effecting the same, which are suitable for the administration of fentanyl or its derivatives continuously through intact skin for the alleviation of pain.

It is accordingly an object of this invention to provide a method for the continuous transdermal administration of fentanyl or its derivatives.

According to the present invention, there is provided a transdermal delivery system for the administration of material selected from fentanyl, and its analgetically effective derivatives which comprises, in combination:

(a) reservoir means containing the base form of said material in amounts sufficient to produce analgesia within four hours of application to intact human skin and deliver said material at a rate sufficient to maintain analgesia for a period of time no less than 12 hours and having a skin proximal surface of a predetermined area, and

(b) means for maintaining said skin proximal surface in drug transmitting relationship to intact human skin.

These and other objects and advantages of our invention will be readily apparent from the following description with reference to the accompanying drawings wherein:

60 *Figure 1* is a cross-section through a schematic, perspective view of one embodiment of transdermal therapeutic system according to this invention, prior to application to the skin.

Figure 2 is a cross-section view through another embodiment of this invention.

Figure 3 is a cross-section view through another embodiment of this invention.

Figure 4 is a plot of *in vitro* skin flux v time for a specific embodiment of this invention.

65 *Figure 5* is a plot of the *in vitro* skin flux v time for another specific embodiment of this invention,

Figure 6 is a plot of the *in vitro* fluxes v time for other specific embodiments of this invention, Figure 7 is a plot of the *in vitro* skin fluxes v time for other specific embodiments of this invention, and Figure 8 is a plot of the *in vitro* skin fluxes v time for another specific embodiments of this invention.

5 Description of the invention

According to the our invention we have found that fentanyl or its derivatives may be administered to the human body via the transdermal route for the purpose of inducing analgesia, if administered through about 5 - 100 cm² and preferably about 10-50cm² of intact skin over an extended period of time at a rate within the range of about 0.5 to 10µg/cm²/hour and preferably at a rate within the range of approximately 10 1-5µg/cm²/hour. When so delivered it is possible, by appropriate selection of the surface area of the drug delivery device to obtain total drug input rates which provide an adequate range of tetration for individual patient needs while maintaining a safe and effective dosage form. Steady-state administration rates obtainable according to this invention range from about 10-300µg/hr and preferably from about 25-150µg/hr. Administration is maintained for at least 12 hours and for up to 7 days with a 1-3 day regimen 15 being considered preferable.

We have found that there is a relatively wide range of permeability of normal human skin to fentanyl and this permeability not only varies from individual to individual and site to site but is also highly dependent on the chemical form of the drug. We have discovered that fentanyl citrate, the form in which fentanyl is presently administered, has such a low skin permeability that it is not at all suitable for trans- 20 dermal delivery even with the use of permeation enhancers. Instead we have found that, in order to obtain the delivery rates noted above, the drug should be incorporated in the transdermal therapeutic system in the form of the base. Our data indicate the permeability of normal human skin to fentanyl base is approximately 4 ± 1.8 (S.D.)µg/cm²/hr with observed extremes of 1.2 and 5.7µg/cm²/hr.

With respect to the other fentanyl derivatives noted above we believe the following relationships between relative permeability and potency to exist: 25

TABLE 1

	DRUG	RELATIVE POTENCY (Fentanyl = 1)	
30			30
	1) Fentanyl	1	
	2) Sufentanyl	15	
35	3) Carfentanyl	34	35
	4) Lofentanyl	15	
	5) Alfentanyl	0.25	

40 Relative Skin Permeability (1) > (2) ≥ (3) > (4) > (5) 40

These relationships allow for therapeutic transdermal administration of these fentanyl derivatives within the parameters set forth herein.

While our invention contemplates the delivery of fentanyl in therapeutic amounts for continuous pe- 45 riods from matrix type transdermal system which rely primarily on skin permeability to control drug input rate, preferred embodiments deliver the drug from rate controlled transdermal system in which the system itself controls the maximum rate at which the drug is delivered through the skin.

The flux, J_{net}, of drug delivered through the skin from a rate controlled transdermal therapeutic system is given by the following relationship: 50

$$\frac{1}{J_{net}} = \frac{1}{J_{skin}} + \frac{1}{J_{system}} \quad (1)$$

55 Thus, in order to provide a transdermal therapeutic system in which at least 50% (and preferably more) of the rate control is provided by J_{system}, the flux from the system into an infinite sink, it is necessary to substantially increase, J_{skin}, the flux through the skin by use of a skin permeation enhancer. Suitable permeation enhancers include without limitation ethanol and other higher alcohols, N-decylmethylsulfoxide (nDMS), polyethylene glycol monolaurate, dilaurate and related esters, glycerol mono-oleate and related mono, di and trifunctional glycerides, diethyl toluamide, A zone® a product of Nelson Research Corp., N, N-dimethyl lauramide, N, N-dimethyl lauramine oxide, and the like, for example. 60

Since a conservative analysis of the existing data suggests that the permeability of normal skin to fentanyl base is in the range of about 1 to 10µg/cm²/hr with most skin being in the range of about 2-5µg/ 65 cm²/hr, sufficient permeation enhancer should preferably be provided for rate controlled systems to in-

crease J_{skin} of the lowest permeability skin to a value no less than J_{system} . Application of formula (1) clearly shows that as J_{skin} increases with J_{system} remaining constant, J_{net} will approach that of J_{system} itself. Thus, sufficient permeation enhancer should preferably be delivered to increase the permeability of even the most impermeable skin to a value at least equal to J_{system} . This will produce a system in which at least 50% of J_{net} is controlled by the system. It would be preferable if the system be at least 70% controlling and this objective can be obtained if the permeability of skin is increased to at least 2.4 times the steady state J_{system} .

When transdermal systems, according to this invention, are applied to the skin, the drug will be transferred from the system into the skin where it is absorbed into the bloodstream to produce its systemic analgetic effect. We have found that skin contains fentanyl binding sites which must be saturated before any significant absorption into the bloodstream occurs. The variation from individual to individual, and site to site appears to lie in the range of about 25-75 $\mu\text{g}/\text{cm}^2$ of the base formed fentanyl or its derivatives and the initial saturation of these sites should proceed rapidly in order to provide rapid onset of analgesia. Since most transdermal therapeutic systems exhibit an initial transitory, increased release of drug which occurs at a significantly higher rate than the steady-state rate later obtained, inclusion of additional amounts of the drug at the skin contacting surface of the device is not an absolute requirement. The systems described herein are capable of delivering drug at initial rates which should induce the onset of analgesia within from two to four hours after application but drug can be added to the adhesive layer or other skin contacting layer to more rapidly saturate the binding sites, if desired.

The skin binding sites are also significant in establishing an upper limit on the size of the transdermal therapeutic system and, conversely, the lower limit on the usable delivery rate. The total amount of drug contained in the binding sites is directly proportional to the surface area of the delivery system and is independent of the rate at which the drug is delivered. When a maximum sized, 100 cm^2 system according to this invention is employed, the total amount of drug within the binding sites could be from at least 2.5 to 7.5 mg. When such a system is removed the total amount of bound drug must be absorbed by the body before the action of the drug stops. In view of the high potency of fentanyl and its derivatives, it is preferable that the amount of drug solubilized in the skin be maintained at or below 3.75 mg level to permit prompt termination of therapy.

When continuous analgesia is desired the depleted system would be removed and a fresh system is applied to a new location. Since saturation of the skin binding sites usually occurs at substantially the same rate as absorption of bound drug, blood levels will remain substantially constant.

Having thus generally described the requirements for transdermal therapeutic systems for administering the base form of fentanyl and its derivatives and methods for their transdermal administration, the following description of various specific embodiments of the invention are provided.

Referring now to Figure 1 a preferred embodiment of a transdermal therapeutic system 1 according to this invention comprises a pouch formed from an impermeable backing 2, a rate controlling membrane 3, and an amine resistant contact adhesive layer 4, covered by a strippable protective backing 5. The impermeable backing 2 is configured to provide a central volume which contains a drug reservoir 6 in the form of a gel having dissolved and suspended drug therein. Although preferred embodiments of this invention utilize an amine resistant in-line adhesive as shown in Figure 1 other means for maintaining the system on the skin can be employed. Such means include a peripheral ring of adhesive outside the path of drug from the system to the skin, in which case the adhesive need not be amine resistant. The use of adhesive overlays or other fastening means such as buckles, belts, and elastic arm bands is also contemplated.

The aforementioned patents describe a wide variety of materials which can be used for fabricating the various layers of the transdermal fentanyl delivery systems according to this invention. This invention therefore contemplates the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions.

Various drug reservoir compositions can be utilized according to this invention and include both aqueous and non-aqueous systems. A general formulation for the preferred aqueous gel system is shown in Table 2 with the gelling agent being hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose or other known gelling agents.

TABLE 2

GEL RESERVOIR COMPOSITION (W/W%)

Material	Broad Range	Preferred Range
Ethanol 95%	0-47	20-35
Gelling Agent	1-10	1-5
Base form of Drug	0.1-10	0.1-2%
H ₂ O	Balance	Balance

The water-ethanol systems described in Table 2 possess certain unique characteristics when used in combination with rate controlling membranes such as low density polyethylene (LDPE), ethylene-vinyl acetate (EVA) copolymers, (0-40% and preferably 5-18% VA) heat sealable polyesters, and elastomeric polyester block copolymers such as the HYTREL[®] polymers available from DuPont and described in U.S. Patent 4,127,127 which is incorporated herein by reference which exert substantial control on the fentanyl release rate without significantly effecting the ethanol release rate. This produces a dynamic situation in which the relative concentration of the ethanol in the reservoir changes with respect to the relative concentration of water and drug as the system is used. Since fentanyl and its derivatives are substantially more soluble in ethanol than water, the thermodynamic activity of the drug in the reservoir does not decrease as would normally be expected as the drug is delivered from the system. The driving force causing the drug to migrate through the rate controlling membrane is the thermodynamic activity of the drug in the solvent rather than the absolute concentration. Thus, the more rapid depletion of the ethanol causes the saturation concentration of the drug in the aqueous reservoir to decrease. By appropriate adjustment of the ethanol and drug delivery rates from the system, the activity of the drug can be maintained constant or even caused to increase during the lifetime of the system.

The rate controlling membrane can be from about 0.5-5 mils (.0127-.1270 mm) thick and preferably about 1-3 mils (0.25-.076 mm) thick. To provide adequate system life, the gel loading will be from about 10-50 mg/cm² yielding a dry loading of from about 0.01-5 mg/cm².

Referring now to Figure 2, a multilaminate type of transdermal therapeutic system according to this invention as shown. Such a transdermal therapeutic system 11 comprises a plurality of lamina bonded together into a unitary structure. The uppermost lamina 12 comprises the backing member, lamina 16 comprises a polymeric drug reservoir, lamina 13 comprises a rate controlling membrane and lamina 14 comprises an amine resistant contact adhesive. Layer 15 is a strippable backing member adapted to be removed prior to use. Elements 12, 13, 14 and 15 may be made from materials similar to those used in the corresponding elements of Figure 1 whereas layer 16 is preferably a polymeric material, which may be plasticized and contain permeation enhancers, in which the drug is dissolved and dispersed. A typical formulation for a laminated transdermal system is shown in Table 3 the rate controlling membrane preferably being selected from the materials noted above as well as from microporous materials.

TABLE 3

LAMINATED SYSTEM

MATERIAL	W/W %
<i>Reservoir</i>	
Polyisobutylene plasticized with mineral oil (PIB/MO) or Silicone polymer	50-95%
Base Form of Drug	5-50%
<i>Contact Adhesive</i>	
PIB/MO, or Amine resistant silicone 0.025-0.076mm	

Another embodiment of this invention is shown in Figure 3 in which the transdermal therapeutic system 21 is a simple monolith. The system 21 comprises a backing member 22 which is impermeable to the fentanyl, a release liner 25 similarly impermeable and adapted to be readily removed from the drug reservoir/contact adhesive layer 23 which consists of a contact adhesive having the drug dissolved in, and if desired, dispersed therethrough. Such a system has the advantage of being easily fabricated, but in the absence of a rate controlling membrane, delivers drug at a rate which is determined primarily by the permeability of the skin at the site of application on the particular individual. Thus, while this system can be employed to provide drug delivery rates within the ranges described herein, the actual delivery rate cannot be as precisely controlled as would be with the systems described generally in Figures 1 and 2. Suitable materials for fabricating of the contact adhesive/reservoir layer include EVA polymers having approximately 0 to 18% vinylacetate content and polyisobutylene/mineral oil containing from 15 to 25% high molecular weight polyisobutylene (an average molecular weight 1,200,000) 20 to 30% low molecular weight polyisobutylene (average molecular weight 35,000) and balance of light mineral oil having a viscosity at 38°C of approximately 10 centipoise. In addition to the drug, the drug reservoir-contact adhe-

sive layer can also contain additives, permeation enhancers and other materials as are generally known to the art.

Specific examples of various transdermal therapeutic systems according to our invention which are capable of administering fentanyl at the desired rates for extended periods of time will be described in the examples set for hereinafter. However, in order for the residual drug in depleted systems to be minimized, we have discovered that the initial concentration of the fentanyl in the matrix material should be selected such that it is less than 0.5mg/cm². For this reason the aqueous-ethanol reservoir systems which permit unit activity to be achieved at this low concentration are presently considered preferable according to our invention. In the following examples all percentages are by weight unless noted. The examples are included by way of illustration only.

Example 1

Transdermal therapeutic systems according to Figure 1 utilizing an aqueous ethanolic gel reservoir were prepared in 10, 20 and 40cm² sizes. Fentanyl base was added to 95% ethanol and stirred to dissolve the drug. Purified water was added to the ethanol-fentanyl solution in amounts sufficient to generate a mixture containing 14.7mg/g of fentanyl in a 30% ethanol-water solvent. Two percent of hydroxyethyl cellulose gelling agent was added to this solution slowly with stirring and mixed until a smooth gel was obtained (approximately one hour). A 0.05mm thick contact adhesive layer was formed on a fluorocarbon-diacrylate treated polyester film which comprised the release liner for the system by solution casting an amine resistant silicone medical adhesive onto the polyester film from a solution in trichlorotrifluoroethane. A 0.05mm thick rate controlling membrane comprised of EVA (9% VA) was pressure laminated to the exposed adhesive. A backing member comprised of a multilaminate of polyethylene, aluminum, polyester and EVA was also provided and the aqueous gel pouched between the backing member and the release liner adhesive/rate controlling membrane on a rotary heat-seal machine at a gel loading of 15mg/cm². Sealed pouches in the sizes of 10,20 and 40 cm² were die cut and immediately pouched to avoid loss of ethanol. The pouched systems were allowed to equilibrate for at least two weeks in order to reach equilibrium concentration of the drug and ethanol in the rate controlling and adhesive layers. After this time the drug reservoir no longer contained any excess drug and the drug concentration in the reservoir had reduced to 8.8mg/g, the saturation concentration of fentanyl in 30% ethanol. The *in vitro* fentanyl flux through cadaver skin into an infinite aqueous sink at 32°C was measured and is shown in Figure 4. As can be seen the fentanyl flux rapidly increased to approximately 1.35µg/cm²/hr in slightly more than four hours and remained substantially constant thereafter. The saturation of the drug in skin occurred during the time the drug flux was increasing to its steady state value. After operation for approximately 24 hours substantially all of the ethanol will have been delivered and the transport rate of fentanyl through skin will have been reduced to the level obtained when no ethanol is present. It would be desirable that the use of this system be discontinued at that point. The systems originally contained approximately 200µg/cm² of fentanyl and over the 24 hour useful life delivered approximately 50µg/cm² resulting in a delivery of approximately 25% of the original drug loading.

Example 2

Systems similar to those described in Example 1 were fabricated except that the drug reservoir contained 47 weight percent ethanol in water and fentanyl base at 3.2mg/gm. The original drug gel loading was 26 mg/cm² and the control membrane was a 0.038mm EVA film (12% VA). The *in vitro* transport rate through skin is shown in Figure 5. As can be seen these systems took longer to achieve steady-state due to the original lower activity (46%) of the fentanyl but, as fentanyl activity increased due to the transport of ethanol from the system a substantially constant steady-state release of approximately 4.5µg/cm² was maintained for 70 hours.

Example 3

Systems similar to those described in Example 1 are manufactured differing from Example 1 in that the original gel concentration contains 20 weight percent ethanol with a fentanyl loading of 8.2 mg/g and are fabricated into systems having a gel loading of 25 mg/cm². After the equilibrating period the drug concentration will fall to approximately 4.2 mg/g in the reservoir with the remainder equilibrating into the adhesive and the rate controlling membrane. After affixation to skin for approximately 24 hours the fentanyl concentration will have decreased to approximately 50 g/gm. As a result of the delivery of both alcohol and fentanyl from the system, the concentration of the fentanyl in the system after approximately 72 hours will be at the saturation concentration in the then remaining aqueous solution containing no more than about 5% ethanol. At this point in time the system would be discarded and would have a residual drug loading of less than 25µg/cm². This results in a higher percentage of drug delivery than in the preceding systems.

Example 4

A multilaminate transdermal therapeutic system of the type described with respect to Figure 2 was prepared by adding low molecular weight polyisobutylene PIB (average molecular weight of 35,000) and high molecular weight PIB (average molecular weight 1,200,000) to a stirring vessel in a ratio of 1.25 to 1.

Light mineral oil (MO) was added to the same vessel with a ratio of approximately 1.125 to 1 part of (PIB). Heptane was added and the mixture was stirred until the polymers dissolved. Sufficient fentanyl base was added to the solution to generate a blend of 20 percent fentanyl in the PIB/MO. The polymer-drug blend was solvent cast onto an occlusive backing such as described in Example 1 and allowed to
 5 evaporate to form approximate 0.05mm thick drug reservoir. Microporous polypropylene film saturated with mineral oil was pressure laminated to the reservoir layer. A PIB/MO mixture as described above but containing sufficient additional fentanyl to provide a 2 percent loading of fentanyl as undissolved solid was cast in a layer approximately 0.05mm thick on a siliconized polyester release liner film and the thus
 10 formed composite laminates were laminated together to form a device as shown in Figure 3. Individual systems were die cut from this laminated film in the sizes of 2.5, 5, 10 and 20 cm circles and were pack- aged. The *in vitro* fentanyl flux from the systems produced according to this example through cadaver skin at 32°C into an infinite sink are shown in Figure 6. Samples differing from those described above by having a solid drug loading of 3.2% were also fabricated. As can be seen from Figure 6, 2% solid drug was adequate to produce a rapid onset of therapy without an unnecessarily high initial drug release rate
 15 and after the initial transitory period both systems provide a steady release rate of approximately 1.8µg/cm²/hr for up to 70 hours.

Example 5

A monolithic system according to Figure 3 was fabricated by preparing a PIB/MO fentanyl base mixture as set forth in Example 4 which was solvent cast onto an occlusive backing and after evaporation of the solvent, laminated to the siliconized release liner. The PIB matrices were fabricated at 10, 20 and 30 percent fentanyl loading and drug transport rates from such systems through human cadaver skin at 32° into an infinite sink were measured. The results are shown in Figure 7. The systems showed the typical time dependent drug release rates from a monolith however continued delivery at a relatively constant rates
 25 through skin for up to 80 hours within the ranges required according to this invention.

Example 6

A monolithic system similar to that described in Example 5 was fabricated using Dow Corning amine resistant silicone adhesive and 20 centistoke silicone medical fluid having 10 and 20 percent fentanyl
 30 base dispersed therein. Drug permeation rates from such systems through cadaver skin into an infinite sink are shown in Figure 8.

Example 7

The effect of ethanol concentration on the permeability of cadaver skin to fentanyl base was investi-
 35 gated by measuring the *in vitro* drug permeation rates through cadaver skin into an infinite sink for systems containing various concentration of ethanolic gels with the results shown in Table 4.

TABLE 4

	% Ethanol	Fentanyl Skin Flux (Jnet)	
40	47%	8.7	40
	30%	4.5	
45	20%	4.8	45
	0-10%	3.71	

Based on these data it appears that about 40% ethanol is required to produce a significant increase in
 50 skin permeability and that at least about 20% ethanol should be employed in a rate controlled aqueous ethanol system to impart a significant degree of control of drug to the systemic circulation.

Having thus generally described our invention and described certain specific embodiments thereof including the embodiment that applicants considered to be the best mode of practicing their invention; it will be readily apparent that various modifications to the invention may be made by workers skilled in
 55 the art without departing from the scope of this invention which is limited only by the following claims wherein:

CLAIMS

- 60 1. A transdermal delivery system for the administration of material selected from fentanyl, and its analgetically effective derivatives which comprises, in combination:
 - (a) reservoir means containing the base form of said material in amounts sufficient to produce analgesia within four hours of application to intact human skin and deliver said material at a rate sufficient to maintain analgesia for a period of time no less than 12 hours and having a skin proximal surface of a
 65 predetermined area, and

- (b) means for maintaining said skin proximal surface in drug transmitting relationship to intact human skin.
2. The transdermal therapeutic system of claim 1 wherein said system is adapted to deliver the base form of the material through intact skin at a rate in the range of from 10 to 300 $\mu\text{g/hr}$ for a substantial portion of said period of time. 5
3. The transdermal therapeutic system of claim 1 or 2 wherein said reservoir means contains a skin permeation enhancer for said material.
4. The transdermal delivery system of any preceding claim wherein said predetermined area is in the range of about 5-100 cm^2 and the rate of delivery of said material is in the range of about 0.5-10 $\mu\text{g/cm}^2/\text{hr}$. 10
5. The transdermal delivery system of claim 4 wherein said area is in the range of about 10-50 cm^2 and said delivery rate is in the range of about 1-5 $\mu\text{g/cm}^2/\text{hr}$.
6. The transdermal delivery system of any preceding claim wherein said material is fentanyl base.
7. The transdermal delivery system of claim 1 wherein: said reservoir means has a skin proximal releasing surface area in the range of about 5-100 cm^2 said reservoir contains between 0.1 and 50% by weight of the base form of said material in amounts and at a concentration adequate to permit delivery of said material through intact human skin at a rate within the range of from 0.5 to 10 $\mu\text{g/cm}^2/\text{hr}$ for at least about 12 hours. 15
8. The transdermal delivery system of claim 7 wherein said means for maintaining said reservoir in material transmitting relationship to the skin is in amine resistant adhesive disposed in the flow path of the material from the reservoir to the skin. 20
9. The transdermal delivery system of claim 7 further comprising release rate controlling means disposed in the flow path of said material to the skin which means limit the flux of material from said system to a level less than the flux of material through the skin to which it is applied.
10. The transdermal delivery system of claim 8 or claim 9 further comprising permeation enhancer means for increasing the permeability of the skin to which said system is applied to said material. 25
11. The transdermal delivery system of claim 10 wherein said permeation enhancer means is admixed in said reservoir means.
12. The transdermal delivery system of claim 11 wherein said release rate controlling means restricts the flux of said material from said system substantially more than the flux of said permeation enhancer from said system. 30
13. The transdermal delivery system of claims 9 to 12 wherein said reservoir is an aqueous gel comprising approximately from 0-47% of 95% ethanol, 1-10% gelling agent, 0.1-10% of said material.
14. The transdermal delivery system of claim 13 wherein said aqueous gel comprises from approximately 20-35% of said ethanol, 1-5% gelling agent and 0.1-2% of said material. 35
15. The transdermal delivery system of claim 14 wherein said release rate controlling means is substantially more permeable to ethanol than to said material.
16. The transdermal delivery system of claim 15 wherein said material is initially contained in said reservoir at equilibrated levels no greater than 0.5 mg/cm^2 .
17. The transdermal system of claim 16 wherein said means for maintaining said system on the skin is an amine resistant adhesive disposed on said release rate controlling means and said material is fentanyl. 40
18. The transdermal delivery system of claim 17 wherein said surface area is in the range of from about 10-50 cm^2 .
19. The transdermal delivery system of claim 18 wherein said reservoir is a polymeric matrix having said material contained therein in an amount from about 5-50% by weight. 45
20. The transdermal delivery system of claim 19 wherein said matrix is selected from polyisobutylene and silicone polymers.
21. The transdermal delivery system of claim 20 wherein said system further comprises release rate controlling means disposed in the flow path of said material to the skin which limits the flux of said material from said system to a level less than the flux of material through the skin to which it is applied. 50
22. The transdermal delivery system of claim 7 wherein said release rate is in the range of from about 1-5 $\mu\text{g/cm}^2/\text{hr}$ and said material is fentanyl.
23. A transdermal delivery system according to claim 1 and substantially as hereinbefore set forth with reference to, and/or as illustrated in the accompanying drawings. 55